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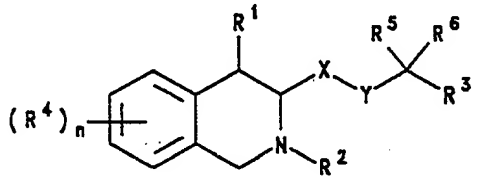
(54) Tetrahydroisoquinoline derivatives

(57) Compounds of formula (I), and salts and prodrugs thereof



(I)

wherein:
R^1 is H, C_{1-6}alkyl or optionally substituted phenyl;
R^2 is H, C_{1-6}alkyl, COR^7, $COOR^7$, $CONHR^7$ or optionally substituted phenylC_{1-4}alkyl; R^7 is C_{1-6}alkyl or optionally substituted phenyl;
R^3 is optionally substituted phenyl;
each R^4 is C_{1-6}alkyl, C_{1-6}alkoxy, halo or trifluoromethyl;
R^5 is H or C_{1-6}alkyl;
R^6 is H, C_{1-6}alkyl or optionally substituted phenyl;
n is 0, 1 , 2, 3 or 4;
X is CH_2 or C=O;
Y is O, S, CH_2 or NR^{10}; where R^{10} is H, C_{1-6}alkyl or COR^5; or X and Y together represent CH=CH; with the proviso that X is not C=O when Y is CH_2;
are tachykinin receptor antagonists useful in therapy.

GB 2 266 529 A

TETRAHYDROISOQUINOLINE DERIVATIVES

This invention relates to a class of compounds which are useful as tachykinin antagonists. More particularly, the compounds of the invention are tetrahydroisoquinoline derivatives.

The tachykinins are a group of naturally occurring peptides found widely distributed throughout mammalian tissues, both within the central nervous system and in peripheral nervous and circulatory systems.

The structures of three known mammalian tachykinins are as follows:

Substance P:

Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met-NH_2

Neurokinin A:

His-Lys-Thr-Asp-Ser-Phe-Val-Gly-Leu-Met-NH_2

Neurokinin B:

Asp-Met-His-Asp-Phe-Phe-Val-Gly-Leu-Met-NH_2

For example, substance P is believed inter alia to be involved in the neurotransmission of pain sensations [Otsuka et al, "Role of Substance P as a Sensory Transmitter in Spinal Cord and Sympathetic Ganglia" in 1982 Substance P in the Nervous System, Ciba Foundation Symposium 91, 13-34 (published by Pitman) and Otsuka and Yanagisawa, "Does Substance P Act as a Pain Transmitter?" TIPS (Dec. 1987) 8 506-510], specifically in the transmission of pain in migraine (B.E.B. Sandberg et al, J. Med Chem, (1982) 25 1009; S.L. Shepheard et al., Br. J. Pharmacol. (1993), 108, 11-12) and in arthritis [Levine et al in Science (1984) 226 547-549]. These peptides have also been implicated in gastrointestinal (GI) disorders and diseases of the GI tract such as inflammatory bowel disease [Mantyh et al in

Neuroscience (1988) 25 (3) 817-37 andD. Regoli in "Trends in Cluster Headache" Ed. Sicuteri et al Elsevier Scientific Publishers, Amsterdam (1987) page 85)]. It is also hypothesised that there is a neurogenic mechanism for arthritis in which substance P may play a role [Kidd et al "A Neurogenic Mechanism for Symmetrical Arthritis" in The Lancet, 11 November 1989 and Grönblad et al "Neuropeptides in Synovium of Patients with Rheumatoid Arthritis and Osteoarthritis" in J. Rheumatol. (1988) 15(12) 1807-10]. Therefore, substance P is believed to be involved in the inflammatory response in diseases such as rheumatoid arthritis and osteoarthritis [O'Byrne et al in Arthritis and Rheumatism (1990) 33 1023-8]. Other disease areas where tachykinin antagonists are believed to be useful are allergic conditions [Hamelet et al Can. J. Pharmacol. Physiol. (1988) 66 1361-7], immunoregulation [Lotz et al Science (1988) 241 1218-21 and Kimball et al, J. Immunol. (1988) 141 (10) 3564-9] vasodilation, bronchospasm, reflex or neuronal control of the viscera [Mantyh et al, PNAS (1988) 85 3235-9] and, possibly by arresting or slowing β-amyloid-mediated neurodegenerative changes [Yankner et al Science (1990) 250, 279-82] in senile dementia of the Alzheimer type, Alzheimer's disease and Down's Syndrome.

Substance P may also play a role in demyelinating diseases such as multiple sclerosis and amyotrophic lateral sclerosis [J. Luber-Narod et. al., poster presented at C.I.N.P. XVIIIth Congress, 28th June-2nd July, 1992], and in disorders of bladder function such as bladder detrusor hyper-reflexia (Lancet, 16th May, 1992, 1239).

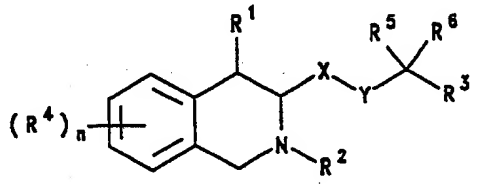
It has furthermore been suggested that tachykinins have utility in the following disorders: depression, dysthymic disorders, chronic obstructive

airways disease, hypersensitivity disorders such as poison ivy, vasospastic diseases such as angina and Reynauld's disease, fibrosing and collagen diseases such as scleroderma and eosinophillic fascioliasis, reflex sympathetic dystrophy such as shoulder/hand syndrome, addiction disorders such as alcoholism, stress related somatic disorders, neuropathy, neuralgia, disorders related to immune enhancement or suppression such as systemic lupus erythmatosis (European patent application no. 0 436 334), ophthalmic disease such as conjuctivitis, vernal conjunctivitis, and the like, and cutaneous diseases such as contact dermatitis, atropic dermatitis, urticaria, and other eczematoid dermatitis (European patent application no. 0 394 989) and emesis (European patent application no. 0 533 280).

In view of their metabolic instability, peptide derivatives are likely to be of limited utility as therapeutic agents. It is for this reason that non-peptide tachykinin antagonists are sought.

Tetrahydroisoquinoline derivatives said to be useful as substance P antagonists are disclosed in WO 92/06079. There is no disclosure of the substitution pattern of the compounds of the present invention.

The present invention provides a compound of formula (I), or a salt or prodrug thereof:



(I)

wherein:

R^1 represents H, C_{1-6}alkyl or phenyl optionally substituted by 1, 2 or 3 groups selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, halo, cyano, nitro, trifluoromethyl, trimethylsilyl, $-OR^a$, SR^a, SOR^a, SO_2R^a, $-NR^aR^b$, $-NR^aCOR^b$, $-NR^aCO_2R^b$, $-CO_2R^a$ or $-CONR^aR^b$;

R^2 represents H, C_{1-6}alkyl, COR^7, $COOR^7$, $CONHR^7$ or phenyl(C_{1-4}alkyl) optionally substituted in the phenyl ring by C_{1-6}alkyl, C_{1-6}alkoxy, halo or trifluoromethyl;

R^3 represents phenyl optionally substituted by 1, 2 or 3 groups selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, halo, cyano, nitro, trifluoromethyl, trimethylsilyl, $-OR^a$, SR^a, SOR^a, SO_2R^a, $-NR^aR^b$, $-NR^aCOR^b$, $-NR^aCO_2R^b$, $-CO_2R^a$ and $-CONR^aR^b$;

each R^4 independently represents C_{1-6}alkyl, C_{1-6}alkoxy, halo or trifluoromethyl;

R^5 represents H or C_{1-6}alkyl;

R^6 represents H, C_{1-6}alkyl or phenyl optionally substituted by 1, 2 or 3 groups selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, halo, cyano, nitro, trifluoromethyl, trimethylsilyl, $-OR^a$, SR^a, SOR^a, SO_2R^a, $-NR^aR^b$, $-NR^aCOR^b$, $-NR^aCO_2R^b$, $-CO_2R^a$ and $-CONR^aR^b$;

R^7 is C_{1-6}alkyl or phenyl optionally substituted by C_{1-6}alkyl, C_{1-6}alkoxy, halo or trifluoromethyl;

n is 0, 1, 2, 3 or 4;

X represents CH_2 or C=O;

Y represents O, S, CH_2, or NR^{10} where R^{10} represents H, C_{1-6}alkyl or COR^7; or X and Y together represent CH=CH; with the proviso that X is not C=O when Y is CH_2; and

R^a and R^b each independently represent H, C_{1-6}alkyl, trifluoromethyl or phenyl optionally substituted by C_{1-6}alkyl, halo or trifluoromethyl.

As used herein, the definition of each expression, when it occurs more than once in any structure, is intended to be independent of its definition elsewhere in the same structure.

The alkyl, alkenyl and alkynyl groups referred to with respect to the above formula may represent straight, branched or cyclic groups or combinations thereof. Thus, for example, suitable alkyl groups include methyl, ethyl, n- or iso-propyl, n-, sec-, iso- or tert-butyl, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, and cycloalkyl-alkyl groups such as cyclopropylmethyl; suitable alkenyl groups include vinyl and allyl; and suitable alkynyl groups include propargyl.

The term "halo" as used herein includes fluoro, chloro, bromo and iodo.

Suitably, R^1 represents unsubstituted or substituted phenyl, preferably unsubstited phenyl.

Suitably R^2 represents H or C_{1-6}alkyl, preferably H or methyl.

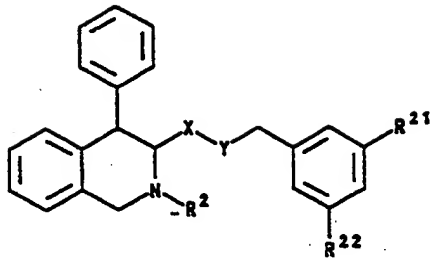
Suitable values for R^4 include, for example, methyl, methoxy, chloro, fluoro and trifluoromethyl.

Preferably R^5 and R^6 are both H.

Preferably n is 0

Preferably Y represents O or NR^{10}, more preferably O.

A particular sub-class of compounds according to the invention is represented by the compounds of formula (IIa), and salts and prodrugs thereof:



(IIa)

wherein:

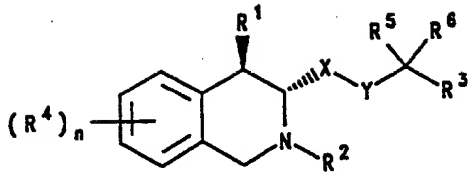
R^2, X and Y are each as defined above with reference to formula (I); and

R^{21} and R^{22} each independently represent H, C_{1-6}alkyl, halo, cyano, nitro, trifluoromethyl, hydroxy, C_{1-6}alkoxy, phenoxy or amino.

Preferred are compounds of formula (IIa) wherein R^{21} and R^{22} are selected from H, methyl, ethyl, t-butyl, methoxy, fluoro, chloro, bromo, iodo and trifluoromethyl. Preferably R^{21} and R^{22} are both other than H, more preferably C_{1-6}alkyl, halo or trifluoromethyl, and are located at the 3- and 5- positions of the phenyl ring. Compounds wherein both R^{21} and R^{22} represent trifluoromethyl are particularly preferred.

A preferred sub-class of compounds according to the invention are those wherein Y represents O.

It is preferred that the substituents R^1 and X- are in the trans orientation, that is to say, the relative stereochemistry indicated in formula (Ia) is preferred:



(Ia)

For use in medicine, the salts of the compounds of formula (I) will be pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds according to the invention or of their pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulphuric acid, oxalic acid, fumaric acid, p-toluenesulphonic acid, maleic acid, succinic acid, acetic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid. Salts of amine groups may also comprise quaternary ammonium salts in which the amino nitrogen atom carries a suitable organic group such as an alkyl, alkenyl, alkynyl or aralkyl moiety. Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include metal salts such as alkali metal salts, e.g. sodium or potassium salts; and alkaline earth metal salts, e.g. calcium or magnesium salts.

The present invention includes within its scope prodrugs of the compounds of formula (I) above. In general, such prodrugs will be functional derivatives of

the compounds of formula (I) which are readily convertible in vivo into the required compound of formula (I). Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

The compounds according to the invention have at least one asymmetric centre, and may accordingly exist both as enantiomers and as diastereoisomers. It is to be understood that all such isomers and mixtures thereof are encompassed within the scope of the present invention.

The invention also provides pharmaceutical compositions comprising one or more compounds of this invention in association with a pharmaceutically acceptable carrier. Preferably these compositions are in unit dosage forms such as tablets, pills, capsules, powders, granules, solutions or suspensions, or suppositories, for oral, parenteral or rectal administration, or administration by inhalation or insufflation.

The invention further provides a process for the preparation of a pharmaceutical composition comprising a compound of formula (I), or a salt or prodrug thereof, and a pharmaceutically acceptable carrier, which process comprises bringing a compound of formula (I), or a salt or prodrug thereof into association with a pharmaceutically acceptable carrier.

For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other

pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a non-toxic pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical

vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone or gelatin.

Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as set out above. Preferably the compositions are adminsitered by the oral or nasal respiratory route for local or systemic effect. Compositions in preferably sterile pharmaceutically acceptable solvents may be nebulised by use of inert gases. Nebulised solutions may be breathed directly from the nebulising device or the nebulising device may be attached to a face mask, tent or intermittent positive pressure breathing machine. Solution, suspension or powder compositions may be administered, preferably orally or nasally, from devices which deliver the formulation in an appropriate manner.

The substance P antagonising activity of the compounds described herein was evaluated using the human NK1R assay described in published European patent application no. 0 528 495. The method essentially involves determining the concentration of the test compound required to reduce by 50% the amount of radiolabelled substance P binding to human NK1R, thereby affording an IC_{50} value for the test compound. The compounds of Examples 1-3 were found to have IC_{50} values less than 1μM.

The compounds of formula (I) are of value in the treatment of a wide variety of clinical conditions which are characterised by the presence of an excess of

tachykinin, in particular substance P, activity. These may include disorders of the central nervous system such as anxiety, depression, psychosis and schizophrenia; neurodegenerative disorders such as dementia, including senile dementia of the Alzheimer type, Alzheimer's disease and Down's syndrome; demyelinating diseases such as multiple sclerosis (MS) and amyotropic lateral sclerosis (ALS; Lou Gehrig's disease) and other neuropathological disorders such as peripheral neuropathy, for example, diabetic or chemotherapy-induced neuropathy, and postherpetic and other neuralgias; respiratory diseases such as chronic obstructive airways disease, bronchopneumonia, bronchospasm and asthma; inflammatory diseases such as inflammatory bowel disease, psoriasis, fibrositis, osteoarthritis and rheumatoid arthritis; allergies such as eczema and rhinitis; hypersensitivity disorders such as poison ivy; ophthalmic diseases such as conjunctivitis, vernal conjunctivitis, and the like; cutaneous diseases such as contact dermatitis, atropic dermatitis, urticaria, and other eczematoid dermatitis; addiction disorders such as alcoholism; stress related somatic disorders; reflex sympathetic dystrophy such as shoulder/hand syndrome; dysthymic disorders; adverse immunological reactions such as rejection of transplanted tissues and disorders related to immune enhancement or suppression such as systemic lupus erythematosis; gastrointestinal (GI) disorders and diseases of the GI tract such as disorders associated with the neuronal control of viscera such as ulcerative colitis, Crohn's disease and incontinence; emesis, including acute, delayed and anticipatory emesis, for example, induced by chemotherapy, radiation, toxins, pregnancy, vestibular disorders, surgery, migraine and variations in intercranial pressure; disorders of bladder

function such as bladder detrusor hyper-reflexia; fibrosing and collagen diseases such as scleroderma and eosinophilic fascioliasis; disorders of blood flow caused by vasodilation and vasospastic diseases such as angina, migraine and Reynaud's disease; and pain or nociception, for example, that attributable to or associated with any of the foregoing conditions, especially the transmission of pain in migraine. For example, the compounds of formula (I) may suitably be used in the treatment of disorders of the central nervous system such as anxiety, psychosis and schizophrenia; neurodegenerative disorders such as senile dementia of the Alzheimer type, Alzheimer's disease and Down's syndrome; respiratory diseases, particularly those associated with excess mucus secretion, such as chronic obstructive airways disease, bronchopneumonia, chronic bronchitis, cystic fibrosis and asthma, and bronchospasm; inflammatory diseases such as inflammatory bowel disease, osteoarthritis and rheumatoid arthritis; adverse immunological reactions such as rejection of transplanted tissues; gastrointestinal (GI) disorders and diseases of the GI tract such as disorders associated with the neuronal control of viscera such as ulcerative colitis, Crohn's disease and incontinence; disorders of blood flow caused by vasodilation; and pain or nociception, for example, that attributable to or associated with any of the foregoing conditions or the transmission of pain in migraine.

The compounds of formula (I) are particularly useful in the treatment of pain or nociception and/or inflammation and disorders associated therewith such as, for example, neuropathy, such as diabetic and chemotherapy-induced neuropathy, postherpetic and other neuralgias, asthma, osteroarthritis, rheumatoid arthritis and especially migraine.

The present invention further provides a compound of formula (I) for use in therapy. According to a further or alternative aspect, the present invention provides a compound of formula (I) for use in the manufacture of a medicament for the treatment of physiological disorders associated with an excess of tachykinins, especially substance P. The present invention also provides a method for the the treatment or prevention of physiological disorders associated with an excess of tachykinins, especially substance P, which method comprises administration to a patient in need thereof of a tachykinin reducing amount of a compound of formula (I) or a composition comprising a compound of formula (I).

For the treatment of certain conditions it may be desirable to employ a compound according to the present invention in conjunction with another pharmacologically active agent. For example, for the treatment of respiratory diseases such as asthma, a compound of formula (I) may be used in conjunction with a bronchodilator, such as a β_2-adrenergic receptor antagonist or tachykinin antagonist which acts at NK-2 receptors. The compound of formula (I) and the bronchodilator may be administered to a patient simultaneously, sequentially or in combination.

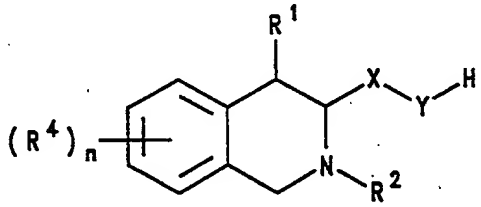
The present invention accordingly provides a method for the treatment of a respiratory disease, such as asthma, which method comprises administration to a patient in need thereof of an effective amount of a compound of formula (I) and an effective amount of a bronchodilator.

The present invention also provides a composition comprising a compound of formula (I), a

bronchodilator, and a pharmaceutically acceptable carrier.

In the treatment of the conditions associated with an excess of tachykinins, a suitable dosage level is about 0.001 to 50 mg/kg per day, in particular about 0.01 to about 25 mg/kg, such as from about 0.05 to about 10 mg/kg per day. For example, in the treatment of conditions involving the neurotransmission of pain sensations, a suitable dosage level is about 0.001 to 25 mg/kg per day, preferably about 0.005 to 10 mg/kg per day, and especially about 0.005 to 5 mg/kg per day. The compounds may be administered on a regimen of 1 to 4 times per day, preferably once or twice per day.

The compounds according to the invention wherein Y is O or S may be prepared by reaction of a compound of formula (III)



(III)

wherein R^1, R^2, R^4 and n are as defined for formula (I), X is CH_2 or C=O, and Y is O or S, with a compound of formula $R^3CR^5R^6Hal$, wherein R^3, R^5 and R^6 are as defined for formula (I), and Hal is halo, such as bromo, chloro or iodo, in the presence of a base.

The reaction is conveniently carried out in a suitable organic solvent, such as an ether, for example, tetrahydrofuran.

Suitable bases of use in the reaction include alkali or alkaline earth metal hydrides, for example, sodium hydride, and alkali metal carbonates, such as caesium carbonate.

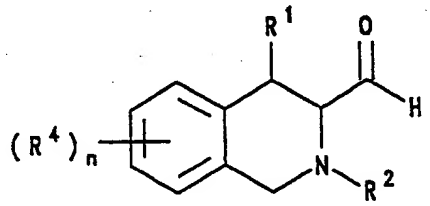
The compounds of the invention wherein Y is a group NR^{10} and X represents C=O may be prepared from the compounds of formula (III) wherein Y is O and X represents C=O by reaction with a compound of formula $R^3CH_2NHR^{10}$, where R^3 and R^{10} are as defined for formula (I), in the presence of a coupling agent, such as dicyclohexylcarbodiimide.

The reaction is suitably effected in an aprotic organic solvent, such as dichloromethane or dimethylformamide, or a mixture thereof.

The compounds according to the invention wherein Y is NR^{10} and X is CH_2 may be prepared from the corresponding compounds of formula (I) wherein X is C=O by reduction.

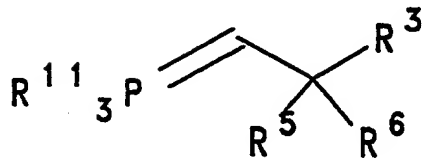
Suitable reducing agents of use in the reaction include borane and metal hydrides, such as lithium aluminium hydride. The reaction is conveniently effected in a suitable orgainc solvent, such as an ether, for example, tetrahydrofuran.

Compounds of formula (I) wherein X and Y together represent CH=CH may be prepared from intermediates of formula (IV)



(IV)

wherein R^1, R^2, R^4 and n are as defined for formula (I), by reaction with a Wittig reagent of formula (V)



(V)

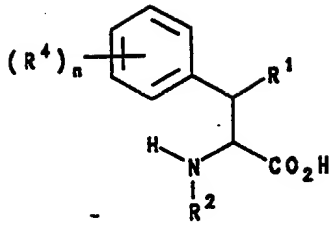
wherein R^3, R^5 and R^6 are as defined for formula (I) and each R^{11} represents a C_{1-6}alkyl, C_{1-6}alkoxy or a phenyl group, in the presence of a base.

Suitable bases include the alkali or alkaline earth metal salts of alcohols, such as, for example potassium t-butoxide.

The reaction is conveniently effected in an inert organic solvent, such as toluene.

Compounds of formula (I) wherein X and Y both represent groups CH_2 may be prepared from the corresponding compounds of formula (I) wherein X and Y together represent CH=CH, by reduction. Suitable procedures and reagents will be readily apparent to persons skilled in the art. For example, the conversion may be achieved using catalytic hydrogenation or dissolving metal reduction with, for example, magnesium in methanol.

Compounds of formula (III) wherein X is C=O and Y is O may be prepared from intermediates of formula (VI)



(VI)

wherein R^1, R^2, R^4 and n are as defined for formula (I), by reaction with formaldehyde in the presence of a mineral acid, such as hydrochloric acid.

Conveniently, the reaction is effected in aqueous solution.

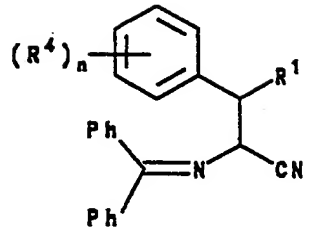
Compounds of formula (III) wherein X is CH_2 may be prepared from the corresponding compounds of formula (III) wherein X is C=O, by reduction, for example, using a metal hydride, such as lithium aluminium hydride.

Compounds of formula (III) wherein Y is S may be prepared form the corresponding compounds wherein Y is O by treating the latter compounds with Lawesson's reagent or phosphorus pentasulphide in a suitable solvent, e.g. pyridine, at ambient or elevated temperature, suitably at the reflux temperature of the chosen solvent.

Intermediates of formula (IV) may be prepared from intermediates of formula (III) wherein X is C=O and Y is O by reduction, for example using a metal hydride reducing agent, such as diisobutylaluminium hydride.

Intermediates of formula (V) are commercially available or can be prepared from the corresponding halides, for example, using the Arbuzov reaction.

Intermediates of formula (VI) may be prepared from compounds of formula (VII)

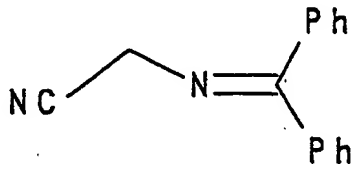


(VII)

wherein R^1, R^4 and n are as defined for formula (I) and Ph represents phenyl, by hydrolysis.

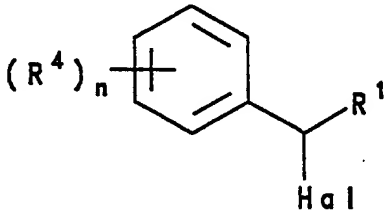
The reaction is conveniently effected by heating a solution of the compound of formula (VII) in concentrated hydrochloric acid at reflux.

Intermediates of formula (VII) may be prepared from the commercially available compound of formula (VIII)



(VIII)

by reaction with compounds of formula (IX)



(IX)

wherein R^1, R^4 and n are as defined for formula (I) and Hal is halo, such as chloro, bromo or iodo, in the presence of a base.

Suitable bases of use in the reaction include metal hydroxides, for example, sodium hydroxide. The reaction is conveniently effected in a mixture of water and a suitable organic solvent, such as a hydrocarbon, for example, toluene, in the presence of a phase transfer catalyst, such as benzyltrimethyl ammonium chloride.

Compounds of formula (IX) may be prepared according to the procedure described by E. J. Corey, Tetrahedron Lett., 1972, 4339, or methods analogous thereto.

Where the above-described process for the preparation of the compounds according to the invention gives rise to mixtures of stereoisomers these isomers may, if desired, be separated, suitably by conventional techniques such as preparative chromatography.

The novel compounds may be prepared in racemic form, or individual enantiomers may be prepared either by enantiospecific synthesis or by resolution. The novel compounds may, for example, be resolved into their component enantiomers by standard techniques, such as the formation of diastereomeric pairs by salt formation with an optically active acid, such as (-)-di-p-toluoyl-d-tartaric acid and/or (+)-di-p-toluoyl-l-tartaric acid followed by fractional crystallization and regeneration of the free base. The novel compounds may also be resolved by formation of diastereomeric esters or amides, followed by chromatographic separation and removal of the chiral auxiliary.

During any of the above synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This

may be achieved by means of conventional protecting groups, such as those described in Protective Groups in Organic Chemistry, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene and P.G.M. Wuts, Protective Groups in Organic Synthesis, John Wiley & Sons, 1991. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

The following Examples illustrate the preparation of compounds according to the invention.

EXAMPLE 1

cis 4-Phenyl-3-(3,5-bis[trifluoromethyl]-1,2,3,4-tetrahydroisoquinoline Hydrochloride

a) Diphenylalaninol

Diphenylalanine methyl ester (6.3g) in dry tetrahydrofuran was added dropwise to a stirred solution of lithium aluminum hydride (986mg) in dry tetrahydrofuran. Once addition was complete the solution was warmed to reflux for one hour and then cooled to room temperature. Water (10ml), 2N sodium hydroxide solution (10ml), and a further aliquot of water (10ml) were added and the solution stirred at room temperature for one hour. The reaction mixture was then filtered through hyflo, diluted with water (100ml) and extracted into ethyl acetate. The organic layers were separated, dried ($MgSO_4$), filtered and the solvent removed under reduced pressure, to afford the product as a clear oil (5.02g). ^1H NMR (360MHz, $CDCl_3$) δ 3.30 (1H, dd, J = 8.0, 3.0Hz, CH<u>H</u>OH), 3.53 (1H, dd, J = 8.0, 1.0Hz, C<u>H</u>H-OH), 3.62 (1H, m, C<u>H</u>-CH_2OH), 3.75 (1H, d, J = 7.0Hz, C<u>H</u>CHCH$_2$OH), 6.9-7.3 (10H, m, ArH). m/z (CI^+) 228.

b) N-t-Butoxycarbonyl diphenylalaninol

Di-t-butyl dicarbonate (5.23g) was added to a stirred solution of diphenylaninol (5.02g) in dichloromethane. The solution was stirred for eighteen hours at room temperature. After this time the solvent was removed under reduced pressure to afford a yellow oil. Recrystallisation from hexane afforded the pure product as yellow needles (3.83g). mp 78-79°C. ^1H NMR

(360MHz, $CDCl_3$) δ 1.34 (9H, s, $C(C\underline{H}_3)_3$), 3.47 (1H, m, $CH\underline{H}$-OH), 3.67 (1H, m, $C\underline{H}H$-OH), 4.13 (1H, d, J = 7.0Hz, $C\underline{H}CHCH_2OH$), 4.46 (1H, m, $CHC\underline{H}CH_2OH$), 4.59 (1H, brs, N$\underline{H}$), 7.13-7.35 (10H, m, ArH); m/z (CI^+) 328.

c) N-t-Butyloxycarbonyl O-[3,5-bis(trifluoromethyl)benzyl] diphenylalaninol

Sodium hydride (288mg, 80%) was added to an ice cold solution of N-t-butoxycarbonyl diphenylalaninol (3.83g) and 3,5-bis(trifluoromethyl)benzyl bromide (3.59g) in dry dimethylformamide. The resulting mixture was allowed to warm to room temperature overnight. The reaction mixture was poured into water and extracted into ethyl acetate. The organic layers were separated, dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Product isolated by flash chromatography as an oil (2.4g). ^1H NMR (360MHz, $CDCl_3$) 1.3 (9H, s, $C(C\underline{H}_3)_3$), 3.3 (1H, d, J = 8.0Hz, $CHCH\underline{H}$-O), 3.45 (1H, d, J = 8.0Hz, $CHC\underline{H}H$-O-), 4.2 (1H, m, $C\underline{H}CH_2$-O-), 4.4-4.6 (3H, m, C$\underline{H}$CH and Ar-$C\underline{H}_2$-O-CH_2CH), 7.1-7.3 (10H, m, ArH), 7.7 (2H, s, CF_3C-C$\underline{H}$-C), 7.8 (1H, s, CF_3C-C$\underline{H}$-CCF_3); m/z (CI^+) 553.

d) O-(3,5-[Bistrifluoromethyl]benzyl diphenylalaninol

Trifluoroacetic acid (25ml) was added to a stirred solution of N-t-butyloxycarbonyl O-[3,5-(bistrifluoromethyl)benzyl] diphenylalaninol (3.49g) in dry dichloromethane. The resulting solution was stirred for two hours at room temperature. The reaction mixture was then partitioned between dichloromethane and saturated sodium carbonate solution. The organic layer was separated, washed with water, dried ($MgSO_4$), filtered and the solvent removed to afford the product as an oil (1.8g). ^1H NMR (360MHz, $CDCl_3$) 3.2 (1H, d, J = 8.0Hz, $CHCH\underline{H}$-O-), 3.5 (1H, d,

J = 8.0Hz, CHC<u>H</u>H-O), 4.15 (1H, m, C<u>H</u>CH_2-O-), 4.4-4.6 (3H, m, C<u>H</u>H and Ar$C\underline{H}_2$-OCH_2CH), 7.0-7.3 (10H, m, ArH), 7.61 (2H, s, CF_3CC<u>H</u>C), 7.68 (1H, s, CF_3CC<u>H</u>CCF_3). m/z (CI^+) 453.

e) <u>N-Formyl O-[3,5-bis(trifluoromethyl)benzyl diphenylalaninol</u>

1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (1.72g) was added to a stirred solution of O-[3,5-bis(trifluoromethyl)benzyl diphenylalaninol (2.54g) and formic acid (7.5ml) in dry dichloromethane. The resulting mixture was stirred at room temperature for six hours and then partitioned between water and dichloromethane. The organic layers were separated, washed with citric acid and water, dried ($MgSO_4$), filtered and solvent removed. Re-crystallisation from ethyl acetate/hexane afforded the product was yellow needles (2.6g). ^{1}H NMR (360MHz, $CDCl_3$) 3.35 (1H, dd, J = 8.0, 1.0Hz, C<u>H</u>H O-CH_2Ar), 3.52 (1H, dd, J = 8.0, 1.0Hz, C<u>H</u>HOCH_2Ar), 4.4 (1H, d, J = 9.0Hz, CH<u>H</u>-Ar), 4.51 (1H, d, J = 4.0Hz, C<u>H</u>-CHCH_2O), 4.58 (1H, d, J = 9.0Hz, C<u>H</u>H-Ar), 5.07 (1H, m, C<u>H</u>-CH_2OCH_2), 5.71 (1H, brd, N<u>H</u>), 7.2-7.3 (10H, m, ArH), 7.7 (2H, s, CC<u>H</u>-CCF_3), 7.79 (1H, s, CF_3C-C<u>H</u>-CCF_3), 8.05 (1H, s, C<u>H</u>O). m/z (CI^-) 481.

f) <u>4-Phenyl, 3-(3,5-bis[trifluoromethyl]benzyloxymethyl 1,2,3,4-tetrahydroisoquinoline hydrochloride</u>

Oxalyl chloride (513mg) was added to a solution of N-formyl O-(3,5-bis[trifluoromethyl]benzyl) diphenylalaninol (1.62g) in dry dichloromethane at room temperature. The resulting solution was stirred for one hour at room temperature, then cooled to -10°C and iron (III) chloride (655mg) added. The reaction was allowed to warm to room temperature overnight,

hydrochloric acid 1N was added and the resulting mixture stirred for one hour. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent removed under reduced pressure to afford a red oil. The recovered material was dissolved in dry methanol and treated with sodium borohydride (150mg) for one hour. After this time the solvent was removed under reduced pressure and the residue subjected to flash chromatography (methanol/chloroform) to afford the purified product as a clear oil. Treatment of the recovered product with ethereal hydrogen chloride and re-crystallisation from methyl-t-butyl ether gave the title compound as a white powder (210mg). mp 189-190°C. ^{1}H NMR (360MHz, DMSO-d6) 3.52 (1H, dd, J = 6.0, 2.0Hz, CHH-NH), 3.74 (1H, dd, J = 6.0, 1.0Hz, CHH-NH), 3.99 (1H, m, CH-CH-NH), 4.63 (1H, d, J = 8.0Hz, CH-CHH-O-CH_2), 4.67 (1H, d, J = 2.0Hz, PhCH-CH), 4.70 (1H, d, J = 9.0Hz, OCHHAr), 4.75 (1H, d, J = 8.0Hz, CH-CHH-OCH_3), 4.80 (1H, d, J = 9.0Hz, OCHHAr), 6.63 (1H, d, J = 3.0Hz, CH-C-CHPh), 7.0-7.3 (9H, m, ArH), 8.03 (1H, s, CF_3C-CH-CCF_3), 8.09 (2H, s, C-CH-CCF_3); m/z (CI^+) 466; $C_{25}H_{21}NOF_6HCl$ $^1/_2$ H_2O requires: C, 58.77; H, 4.54; N, 2.74; Found C, 58.51; H, 4.47; N, 2.77%.

EXAMPLE 2

4-Phenyl-1,2,3,4-tetrahydroisoquinoline-3-[3',5'-bis (trifluoromethylbenzyl)carboxylate

a) 4-Phenyl, 3-carboxy-1,2,3,4-tetrahydroisoquinoline

A solution of diphenylalanine (10.0g), concentrated hydrochloric acid (75ml) and formaldehyde (23ml x 37%) was warmed to reflux for 30 minutes. A further quantity of

concentrated hydrochloric acid (20ml) and formaldehyde (20ml x 37%) was added and heating continued for three hours. The solution was then allowed to cool to room temperature overnight. The product was isolated by filtration. Recrystallisation from ethanol afforded the pure product as white needles mp 160-162°C. ^{1}H NMR (360MHz, DMSO-d6) 4.54 (1H, m, C<u>H</u>CO_2H), 4.6-4.86 (3H, m, 1H C<u>H</u>-Ph and 2H C<u>H</u>$_2$-NH), 8.66 (1H, d, J = 6.1Hz, Ar-C<u>H</u>-CH-CHCO_2H). m/z (CI^+) 253.

b) <u>4-Phenyl-1,2,3,4-tetrahydroisoquinoline-3-[3',5'-bis (trifluoromethylbenzyl)carboxylate</u>

Di-t-butyldicarbonate (370mg) was added to a rapidly stirring suspension of 4-phenyl-3-carboxy-1,2,3,4-tetrahydroisoquinoline (500mg) and K_2CO_3 (700mg) in a mixture of 1,4-dioxan and water (1:1). The resulting solution was stirred for 4 hours, at room temperature, then acidified with citric acid. The reaction mixture was partitioned between water and ethyl acetate. The organic layers were separated, dried ($MgSO_4$), filtered and reduced to dryness. The solid residue was re-suspended in dry methanol and caesium carbonate (211mg) added. The resulting solution was stirred for 30 minutes and then the solvent removed under reduced pressure. The solid residue was re-suspended in dry dimethyl formamide (50ml) and a solution of 3,5-bis(trifluoromethyl)benzyl bromide (240µl) added. The resulting solution was stirred at room temperature overnight. The reaction mixture was poured into water (300ml) and extracted into ethyl acetate. The organic extracts were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. The oily residue was treated overnight with a saturated solution of hydrochloric acid in methanol. Removal of solvent under reduced pressure and re-crystallisation from

ethanol afforded the product as a white powder. mp 175-176°C. ^{1}H NMR (360MHz, DMSO-d6) 4.40 (1H, d, J = 10Hz, Ph-CHH-N), 4.42 (1H, d, J = 8.0Hz, HN-CH-CO_2), 4.61 (1H, d, J = 10Hz, Ph-CHH-N), 4.72 (1H, d, J = 8.0Hz, Ph-CH-CO_2H), 5.2 (2H, m, CO_2CH_2-Ar), 6.6 (1H, d, J = 5.0Hz, Ar-H-CHPh), 7.1-7.25 (10H, m, ArH), 7.8 (2H, s, 2 x C-CH-CCF_3), 8.09 (1H, s, CF_3C-CH-CCF_3); m/z (CI^+) 479; $C_{25}H_{20}NO_2F_6Cl$ requires C, 57.70; H, 3.97; N, 2.69. Found C, 57.70; H, 4.01; N, 2.64%.

EXAMPLE 3

trans-N-Methyl-4-phenyl-3-[3',5'-bis(trifluoromethyl)benzyloxymethyll-1,2,3,4-tetrahydroisoquinoline

a) N-Methyl-4-phenyl 3-carboxy-1,2,3,4- tetrahydro isoquinoline

A solution of diphenylalanine (10.0g), concentrated hydrochloric acid (75ml) and formaldehyde (23ml x 37%) was warmed to reflux for 24 hours. The solution was then allowed to cool to room temperature overnight. The product was isolated by filtration. Recrystallisation from ethanol afforded the pure product as white needles mp 174-178°C. ^{1}H NMR (360MHz, DMSO-d6) 2.19 (3H, s, NCH_3), 4.54 (1H, m, $CHCO_2$H), 4.6-4.86 (3H, m, 1H CH-Ph and 2H CH_2-NH), 8.66 (1H, d, J = 6.1Hz, Ar-CH-CH-$CHCO_2$H). m/z (CI^+) 267.

b) N-Methyl-4-phenyl-3-hydroxymethyl-1,2,3,4-tetrahydroisoquinoline

To a solution of the N-methyl-4-phenyl, 3-carboxy-1,2,3,4-tetrahydroisoquinoline (2.0g) in dry tetrahydrofuran was added

lithium aluminium hydride (1.0M solution in tetrahydrofuran, 7.1ml). The mixture was heated to reflux for two hours, then allowed to cool to 23°C before being quenched with 4N NaOH. Water (10ml) was added. The mixture was filtered through celite, the filtrate was extracted with ethyl acetate. The combined organic fractions were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the product as a yellow oil (1.49g); ^1H NMR (360MHz, DMSO-d6), oxalate salt. δ 2.6 (3H, s), 3.2 (1H, m), 3.45 (2H, m), 3.9-4.2 (2H, q), 4.25 (1H, d), 6.8 (1H, s), 7.73 (8H, m). m/z (E.I.$^+$), 222 (M-31); C.I.$^+$, 254, 222.

c) N-Methyl-4-phenyl-3-hydroxymethyl-1,2,3,4-tetrahydroisoquinoline (1.0g) and 3,5-bis(trifluoromethyl) benzylbromide (1.21g) were dissolved in a 1:1 mixture of dry dimethylformamide and tetrahydrofuran (20ml). To this solution was added sodium hydride (60% in oil, 150mg). After two hours, T.L.C. (3:1, hexane:ethyl acetate) shows no starting material. The mixture was poured into water and extracted with ethyl acetate (2 x 75ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated in vacuo to give a yellow oil. Purified by flash column chromatography (3:1, hexane:ethyl acetate) to give a clear oil. The product was dissolved in ether, hydrogen chloride gas was bubbled through for two minutes. Ether was removed under reduced pressure to give the title compound as a white crystalline solid (210mg). mp 71°C. NMR, 260MHz, free base $CDCl_3$. δ 2.5 (3H, s), 3.9 (1H, m), 3.5 (2H, m), 4.2 (1H, d), 4.5 (2H, q), 6.8 (1H, d), 7.74 (8H, m), 7.7 (2H, s), 7.8 (1H, s). m/z, (CI$^+$), 480, 481. ($C_{26}H_{23}F_6NO.HCl.1^1/_4\ H_2O$) requires C, 58.00, H, 4.96; N, 2.60 Found C, 58.04; H, 5.33; N, 2.48.

The following examples illustrate pharmaceutical compositions according to the invention.

EXAMPLE 4A Tablets containing 1-25mg of compound

	Amount mg		
Compound of formula (I)	1.0	2.0	25.0
Microcrystalline cellulose	20.0	20.0	20.0
Modified food corn starch	20.0	20.0	20.0
Lactose	58.5	57.5	34.5
Magnesium Stearate	0.5	0.5	0.5

EXAMPLE 4B Tablets containing 26-100mg of compound

	Amount mg		
Compound of formula (I)	26.0	50.0	100.0
Microcrystalline cellulose	80.0	80.0	80.0
Modified food corn starch	80.0	80.0	80.0
Lactose	213.5	189.5	139.5
Magnesium Stearate	0.5	0.5	0.5

The compound of formula (I), cellulose, lactose and a portion of the corn starch are mixed and granulated with 10% corn starch paste. The resulting granulation is sieved, dried and blended with the remainder of the corn starch and the magnesium stearate. The resulting granulation is then compressed into tablets containing 1.0mg, 2.0mg, 25.0mg, 26.0mg, 50.0mg and 100mg of the active compound per tablet.

EXAMPLE 5 Parenteral injection

	Amount mg
Compound of formula (I)	1 to 100mg
Citric Acid Monohydrate	0.75mg
Sodium Phosphate	4.5mg
Sodium Chloride	9mg
Water for Injections	to 1ml

The sodium phosphate, citric acid monohydrate and sodium chloride are dissolved in a portion of the water. The compound of formula (I) is dissolved or suspended in the solution and made up to volume.

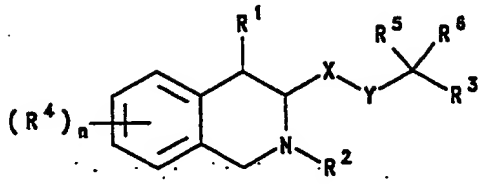
EXAMPLE 6 Topical formulation

	Amount mg
Compound of formula (I)	1-10g
Emulsifying Wax	30g
Liquid paraffin	20g
White Soft Paraffin	to 100g

The white soft paraffin is heated until molten. The liquid paraffin and emulsifying wax are incorporated and stirred until dissolved. The compound of formula (I) is added and stirring continued until dispersed. The mixture is then cooled until solid.

CLAIMS:

1. A compound of formula (I), or a salt or prodrug thereof:



(I)

wherein:

R^1 represents H, C_{1-6}alkyl or phenyl optionally substituted by 1, 2 or 3 groups selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, halo, cyano, nitro, trifluoromethyl, trimethylsilyl, $-OR^a$, SR^a, SOR^a, SO_2R^a, $-NR^aR^b$, $-NR^aCOR^b$, $-NR^aCO_2R^b$, $-CO_2R^a$ and $-CONR^aR^b$;

R^2 represents H, C_{1-6}alkyl, COR^7, $COOR^7$, $CONHR^7$ or phenyl(C_{1-4}alkyl) optionally substituted in the phenyl ring by C_{1-6}alkyl, C_{1-6}alkoxy, halo or trifluoromethyl;

R^3 represents phenyl optionally substituted by 1, 2 or 3 substituents selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, halo, cyano, nitro, trifluoromethyl, trimethylsilyl, $-OR^a$, SR^a, SOR^a, SO_2R^a, $-NR^aR^b$, $-NR^aCOR^b$, $-NR^aCO_2R^b$, $-CO_2R^a$ and $-CONR^aR^b$;

each R^4 independently represents C_{1-6}alkyl, C_{1-6}alkoxy, halo or trifluoromethyl;

R^5 represents H or C_{1-6}alkyl;

R^6 represents H, C_{1-6}alkyl, or phenyl optionally substituted by 1, 2 or 3 substituents selected from the group consisting of C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, halo, cyano, nitro, trifluoromethyl,

trimethylsilyl, $-OR^a$, SR^a, SOR^a, SO_2R^a, $-NR^aR^b$, $-NR^aCOR^b$, $-NR^aCO_2R^b$, $-CO_2R^a$ and $-CONR^aR^b$;

R^7 represents C_{1-6}alkyl or phenyl optionally substituted by a substituent selected from C_{1-6}alkyl, C_{1-6}alkoxy, halo and trifluoromethyl;

n is 0, 1, 2, 3 or 4;

X represents CH_2 or C=O;

Y represents O, S, CH_2, or NR^{10} where R^{10} is H, C_{1-6}alkyl or COR^5; or X and Y together represent CH=CH; with the proviso that X is not C=O when Y is CH_2; and

R^a and R^b each independently represent H, C_{1-6}alkyl, trifluoromethyl or phenyl optionally substituted by C_{1-6}alkyl, halo or trifluoromethyl.

2. A compound according to claim 1 wherein R^1 is substituted or unsubstituted phenyl.

3. A compound according to claim 1 or claim 2 wherein R^2 is selected from H and C_{1-6}alkyl.

4. A compound according to any preceding claim wherein R^3 is phenyl substituted by up to three groups selected from C_{1-6}alkyl, halo and trifluoromethyl.

5. A compound according to any preceding claim wherein Y is selected from O and NR^{10}.

6. A compound according to claim 5 wherein Y is O.

7. A compound according to any preceding claim wherein R^5 and R^6 each represents H.

8. A compound according to claim 1 selected from:
cis 4-phenyl-3-[3',5'-bis(trifluoromethyl) benzyloxymethyl] 1,2,3,4-tetrahydroisoquinoline;
trans N-methyl-4-phenyl-3-[3',5'-bis(trifluoromethyl) benzyloxymethyl] 1,2,3,4-tetrahydroisoquinoline;
trans 3',5'-bis(trifluoromethyl)benzyl 4-phenyl 1,2,3,4-tetrahydroisoquinoline-3-carboxylate;
and salts and prodrugs thereof.

9. A pharmaceutical composition comprising a compound according to any preceding claim in association with a pharmaceutically acceptable carrier therefor.

10. A pharmaceutical composition as claimed in claim 9 further comprising a bronchodilator.

11. The use of a compound as claimed in claim 1 for the manufacture of a medicament for the treatment of a physiological disorder associated with an excess of tachykinins.

12. The use of a compound as claimed in claim 1 for the manufacture of a medicament for the treatment of pain or inflammation.

13. The use of a compound as claimed in claim 1 for the manufacture of a medicament for the treatment or prevention of migraine.

14. The use of a compound as claimed in claim 1 for the manufacture of a medicament for the treatment or prevention of arthritis.

15. The use of a compound as claimed in claim 1 for the manufacture of a medicament for the treatment of postherpetic neuralgia.

atents Act 1977
Examiner's report to the Comptroller under Section 17 (The Search Report)

Application number

GB 9308684.1

Relevant Technical fields

(i) UK Cl (Edition L) C2C

(ii) Int Cl (Edition 5) C07D

Search Examiner

P N DAVEY

Databases (see over)

(i) UK Patent Office

(ii) ONLINE DATABASES: CAS ONLINE

Date of Search

8 JULY 1993

Documents considered relevant following a search in respect of claims

Category (see over)	Identity of document and relevant passages	Relevant to claim(s)
P,X	EP0496369 A1 (HOECHST) 29 July 1992 see example pages 3, 4, 8, 9	1, 3, 5-7
X	EP 0049605 A1 (WARNER-LAMBERT) see example 5, 9, 10	1, 3, 5-7
X	Synth Commun 22(19), 2745-56	1, 3, 5-7
X	Helv Chim Acta 70(7), 1944-54	1, 3, 5-7
X	J Med Chem 29(10) 1953-61	1, 3, 5-7

Category	Identity of document and relevant passages	Relevant to claim(s)

Categories of documents

X: Document indicating lack of novelty or of inventive step.

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